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June 8, 2011 Electronic signature: / Melissa L. Sistrunk /
Date Melissa L. Sistrunk (Reg. No. 45,579)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Makrina D. Savvidou *et al.*
Application No.: 10/553,462 Confirmation No.: 8934
Filed: April 17, 2004 Art Unit: 1632
For: SCREEN FOR PRE-ECLAMPSIA Examiner: A. K. Singh

PRE-APPEAL BRIEF

The Final Office Action of December 9, 2010 ("the Action") maintains two rejections under 35 USC §103(a). Claims 1, 6-7 and 8 are rejected under 35 U.S.C. §103(a) as obvious in view of Holden *et al.* (Am J Obstet Gynecol. 1998; 178(3):551-6; "Holden") in combination with Ellis *et al.* (Acta. Obstr. Gynecol. Scand. 2001: 80, 602-608; "Ellis") and Boger (WO 2002/14873; "Boger"). Claims 1 and 11 are rejected under 35 U.S.C. §103(a) as obvious in view of Holden in combination with Ellis, Boger, and Albaiges *et al.* (Obstet. Gynecol. 2000; 96:559-64; "Albaiges"). The claims concern a method of determining if a pregnant woman is at risk of developing pre-eclampsia or if her fetus is at risk of developing intrauterine growth restriction by measuring asymmetric dimethylarginine (ADMA) in plasma obtained from the woman at 23 to 25 weeks of gestation, wherein if the level is greater than 1.5 µmol/L, the woman and fetus are at risk.

I. Cited Prior Art

The Examiner states that Appellants have attacked references individually instead of addressing the combination of references. Appellants respectfully assert that in the previous Response they in fact did address the combination of references ("…the combination of Holden, Ellis and Boger fails to disclose or suggest.."; page 5 of the Response filed September 22, 2010) and, furthermore, that Appellants must at least address the merits of each cited prior art reference to be able to advance their argument why the combination in a particular rejection fails.

The Examiner further holds that Appellants have set forth "selective reading of the teachings" of Holden in view of Ellis to formulate the grounds for teaching away (page 5 of the Action). Appellants respectfully assert that they have not argued the combination of references selectively but instead focus the Examiner on specific details of the combination of references as they relate to the claimed invention. Appellants respectfully remind the Examiner that a prior art reference must be considered in its entirety, *i.e.*, as a whole, ***including portions that would lead away*** from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Appellants address the respective citations below to clarify their teachings and the Examiner's representations thereof. Appellants address the combination of references in Section III of this paper.

A. Holden

Holden teaches that a level of 1.17 µmol/L is associated with pre-eclampsia in *third* trimester patients. Although the Examiner characterizes Holden as teaching determination of levels of ADMA "…to be around 0.52 µmol/L to 1.17 µmol/L during the second trimester…" (page 3 of the Action), this is a mischaracterization of Holden. The Examiner refers to Fig. 1 of Holden, but this figure only refers to *pre-eclampsia* in the context of the *third* trimester. Appellants' claimed invention clearly recites that the woman is at risk if the levels are greater than 1.5 µmol/L during 23 to 25 weeks, yet all Holden shows is that levels of 0.52 µmol/L in the second trimester are associated with *normotensive* pregnant women, ***not*** *pre-eclamptic* patients.

Furthermore, on page 3 of the Action, the Examiner characterizes Figure 1A as disclosing that "…pregnant woman have pre-eclampsia if ADMA in the plasma sample is 1.25 gmol/L (see figure 1A).." However, Figure 1A concerns mean arterial blood pressure (mm/Hg) and, nevertheless, teaches 125 mmHg for *pre-eclamptic* patients in the *third* trimester.

The Examiner notes that Holden teaches that "…any ADMA level greater than 0.75 µmol/L would also have PE meeting the limitation of this claim." (page 3 of the Action).

Appellants fail to find this disclosure in Holden. All that a skilled artisan can glean from Holden is that if a woman has 1.17 µmol/L *in the third trimester*, this is associated with pre-eclampsia.

B. Ellis

Figure 1 of Ellis demonstrates that the level of ADMA can be assayed at 24 to 32 weeks, and a level between 0.51 and 0.82 µmol/L is associated with pre-eclampsia. However, on page 3 of the Action, the Examiner characterizes Ellis as teaching the measurement of "...ADMA level in plasma of pregnant woman at stage 24-25 weeks gestation and reported that pregnant woman have pre-eclampsia if ADMA in the plasma sample is greater than 0.75 µmol/L (see figure 1)." However, Figure 1 does not show this—it shows that there is severe preeclampsia in a range of 0.51-0.82 µmol/L.

It is noteworthy that Ellis teaches that "Symmetric, but not asymmetric, dimethylarginine correlated to the severity of the condition" (Abstract), so the skilled artisan would find no reason under *KSR* to utilize ADMA in correlation with severe pre-eclampsia. Furthermore, Ellis teaches that the elevation of symmetric dimethylarginine was more pronounced than that of asymmetric dimethylarginine, so based on Ellis, the skilled artisan would be motivated to employ symmetric dimethylarginine alone in the analysis to reduce time and cost. Obviousness requires a suggestion of all the elements in a claim (*CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 [68 USPQ2d 1940] (Fed. Cir. 2003)) and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 [82 USPQ2d 1385] (2007).

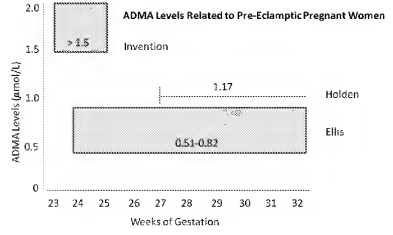
II. The Claimed Invention is Patentable under 35 USC §103

Appellants assert that the claimed invention is patentable over the combination of references, because the combination does not teach, suggest, or provide motivation to modify the references to achieve the claimed invention.

Appellants provide the illustration below to compare the claimed invention to Holden and Ellis in the combination. As illustrated therein, the combination of Holden and Ellis are

mutually exclusive with each other and also with the claimed invention, because they teach measurement of ***incompatible*** ***non-overlapping*** ADMA levels (1.17 μmol/L *vs.* 0.51 to 0.82 μmol/L *vs.* greater than 1.5 μmol/L). The skilled artisan would not obtain "greater than 1.5 μmol/L" from teachings of 1.17 μmol/L **or** 0.51 to 0.82 μmol/L. These are irreconcilable values, and the skilled artisan would not know which value to modify for the combination and whether the level should be raised from 0.82 μmol/L or reduced from 1.17 μmol/L, for example.

Furthermore, the claimed invention has ***mutually exclusive*** gestational windows compared with Holden. The claimed invention clearly concerns 23 to 25 weeks, but Holden teaches assaying in the third trimester. The skilled artisan would not be motivated to alter Holden for such a clear violation of its teaching. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). The skilled artisan from the combination of references would not know whether to monitor pre-eclampsia in the second trimester or third trimester.



The Examiner contends that because Ellis teaches a level of ADMA of 0.8 μmol/L, that the skilled artisan would assume that a higher level of ADMA would put the woman at risk of developing pre-eclampsia (page 6 of the Action). However, the Examiner must meet his own standard of addressing the combination of references, so in the combination of Holden and Ellis, would the disclosure be at or around 1.17 μmol/L, within 0.51-0.82 μmol/L, or greater than 0.8 μmol/L, and would it be in the second or third trimester? In any event, Appellants assert that the representation is not necessarily correct, as Ellis' tested gestational period of 24-32 weeks is outside the claimed invention of 23 to 25 weeks. Even if the skilled artisan would assume that levels higher than 0.8 μmol/L would suggest a risk of pre-eclampsia, there is no indication in the combination of references at which level the risk would be indicative. Would it be greater than 0.9 μmol/L? 1.0 μmol/L? 1.2 μmol/L? The skilled artisan could not be aware of the limit of the level other than what is provided by the specification, so this is improper hindsight reasoning, and under *KSR* the skilled artisan must have a reason to modify the references in the combination to achieve a particular ADMA level.

Finally, Boger and Albaiges fail to cure the defects of their respective rejections. Boger discloses methods for prognosis for sick patients having elevated ADMA and discloses nothing specific about particular levels of ADMA correlating to pre-eclampsia at particular stages of pregnancy. For the rejection that includes Albaiges, this reference concerns use of Doppler diagnosis of pre-eclampsia. Applicants note that claim 1 is included in the rejection with Albaiges, but claim 1 lacks any element concerning Doppler waveform analysis.

Appellants respectfully request that this rejection be withdrawn.

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Respectfully submitted,

By __/Melissa L. Sistrunk/__

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